CHAPTER 2

Formation of All-Carbon Quaternary Centers via Enantioselective Pd-Catalyzed α-Vinylation of γ-Lactams †

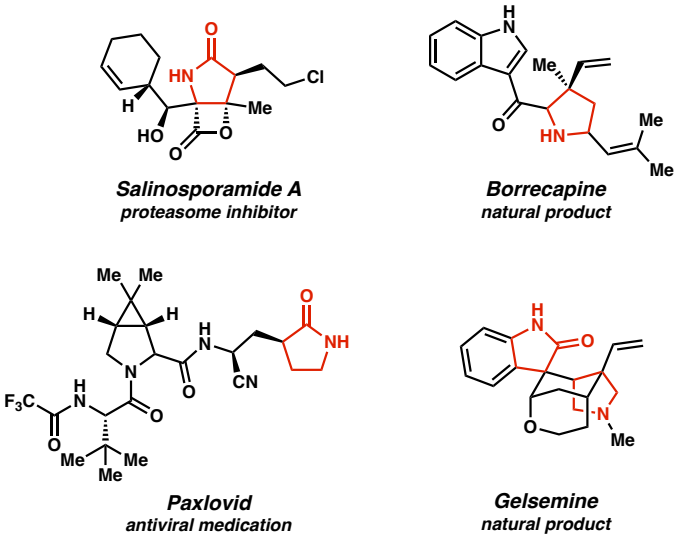
2.1 INTRODUCTION

γ-lactams are heterocyclic motifs that are overrepresented in pharmaceuticals and natural products alike (Figure 2.1).[1,2] The direct vinylation of these materials remains an unsolved problem in organic synthesis, limiting the ability of these structures to be elaborated to more complex scaffolds with potential biological applications. Our group has previously disclosed a novel, Pd-catalyzed strategy toward the α-arylation of PMP-protected γ-lactams containing pre-existing substitution at the α-position.[3] As such, we successfully achieved the first asymmetric α-arylation of γ-lactams forming enantioenriched all-carbon quaternary centers. We imagined that this success could be

† This work was performed in collaboration with Farbod A. Moghadam, Dr. Melinda Chan, Dr. Carina Jette, Dr. Shunya Sakurai, and Dr. Brian M. Stoltz. Portions of this chapter have been reproduced with permission from Moghadam, F. A.; Barbor, J. P.; Chan, M.; Jette, C. I.; Sakurai, S.; Stoltz, B. M. Formation of All-Carbon Quaternary Centers via Enantioselective Pd-catalyzed α-Vinylation of γ-Lactams. *Org. Lett.* **2024**, *26*, 7551–7554.

translated to the more unprecedented vinylation of these nucleophiles, so we commenced with an optimization campaign aimed to effect a Pd-catalyzed vinylation.

Figure 2.1 *Selected examples of γ-lactams of pharmaceutical relevance and natural products.*

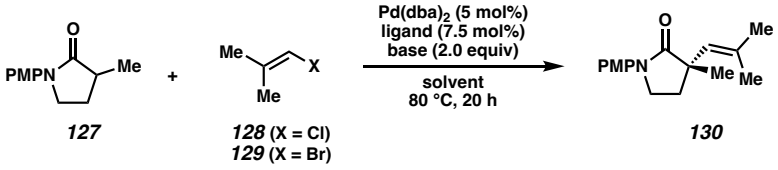


2.2 REACTION OPTIMIZATION

Utilizing the same catalytic conditions disclosed in our prior report, initial optimization efforts illustrated the superiority of vinyl chloride electrophiles and lithium bases (Table 2.1). We observed a severe counterion effect, as use of NaHMDS or KHMDS afforded no desired product, whereas LiHMDS afforded a 46% yield of the desired **130** with an excellent 90% ee. Exploration of similar lithium bases, like LiTMP, garnered diminished results. Similarly, vinyl chlorides were found to be essential for both yield and enantioselectivity, as use of the corresponding vinyl bromide **129** delivered **130** in a diminished 27% yield and 77% ee. Use of the more sterically encumbered ligand **132** did not improve the reaction further. Although initially excited to find that use of CPME resulted in a slight improvement of the ee to 92%, we found that dioxane was ultimately

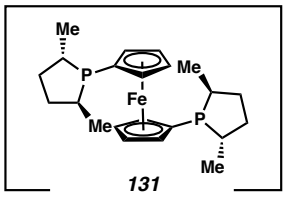
the optimal solvent for this transformation, and dilution of the reaction to 0.05 M allowed for an improved 58% yield and 93% ee.

Table 2.1 *Reaction optimization.*

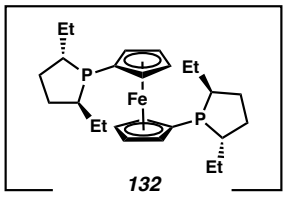


127 ***128*** **(X = Cl)** ***129*** **(X = Br)** ***130***

Entry	Ligand	X	Base	Solvent	Yield (%)	ee (%)
1	131	Cl	NaHMDS	dioxane	0	–
2	131	Cl	KHMDS	dioxane	0	–
3	131	Cl	LiHMDS	dioxane	46	90
4	131	Cl	LiTMP	dioxane	29	ND
5	131	Br	LiHMDS	dioxane	27	77
6	132	Cl	LiHMDS	dioxane	43	88
7[b]	131	Cl	LiHMDS	THF	19	ND
8[b]	131	Cl	LiHMDS	CPME	43	92
9[c]	131	Cl	LiHMDS	CPME	38	ND
10[c]	131	Cl	LiHMDS	dioxane	58	93



131
(*S*,*S*)-Me-Ferrocelane



132
(*S*,*S*)-Et-Ferrocelane

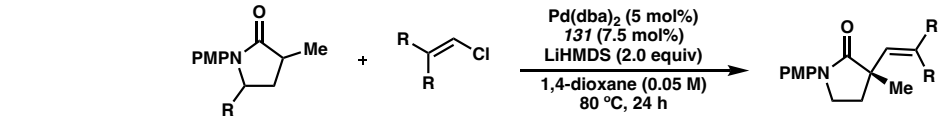
[a] Reactions performed at 0.1 mmol scale and 0.1 M. Yields determined by ^{1}H NMR with CH_2Br_2 internal standard. [b] Reaction performed at 70 ºC for 48h. [c] Reaction performed at 0.05 M concentration.

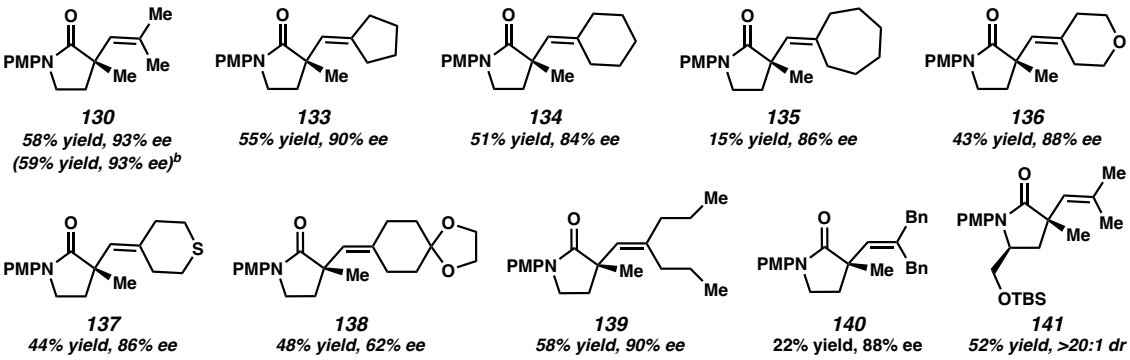
2.3 SUBSTRATE SCOPE

With optimized conditions in hand, we sought to investigate the range of compatible substitution patterns on the vinyl halide coupling partner (Table 2.2). Vinyl electrophiles featuring a cyclopentyl, cyclohexyl and cycloheptyl substitution at the 2,2-position afforded products with high enantioselectivity, although **135** was generated in diminished yield likely due to increased steric hindrance. Additionally, saturated heterocyclic moieties, such as a pyran and thiopyran, were well tolerated. Although acyclic

substrate **139** could also be obtained in comparable yield and ee, **140** was isolated in diminished yield. Substitution at the α-position was limited to methyl, but we were pleased to find that pre-existing substitution at the γ-position of the lactam resulted in a predictable matched/mismatched situation. Enhancement of diastereoselectivity and higher reaction efficiency was observed for product **141**, whereas lower yield and diastereoselectivity was observed for its epimer **154**.[4] We were also able to implement our method at a 3 mmol scale, thereby obtaining over 450 mg of **130** in similar yield and ee.

Table 2.2 *Substrate scope.*[a]





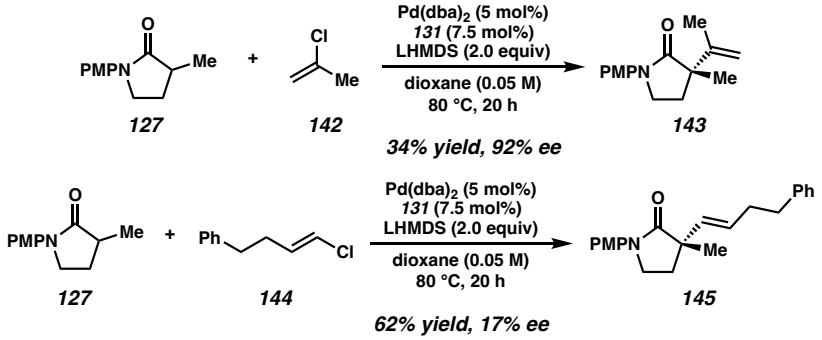
[a] Reactions performed at 0.1 mmol scale. [b] Reaction performed on 3.0 mmol scale. [c] Yields determined by ^{1}H NMR with CH_2Br_2 internal standard.

2.4 PRELIMINARY MECHANISTIC INSIGHTS

While exploring the scope of this transformation, we found that use of 1,1-disubstituted or *trans*-1,2-disubstituted electrophiles resulted in either a diminished yield or enantioselectivity, respectively (Scheme 2.1). Hypothesizing that reductive elimination is both inner-sphere and enantiodetermining,[5,6] we posit that the diminished yield of the

1,1-disubstituted electrophiles originates from steric congestion at the metal center, which may deter transmetalation of the lithium enolate to palladium. Conversely, we propose that the greatly minimized interactions between the ligand and *trans*-1,2-disubstituted electrophiles result in high conversion but with poor enantiocontrol.

Scheme 2.1 *Reaction with 1,1- and 1,2-disubstituted electrophiles.*



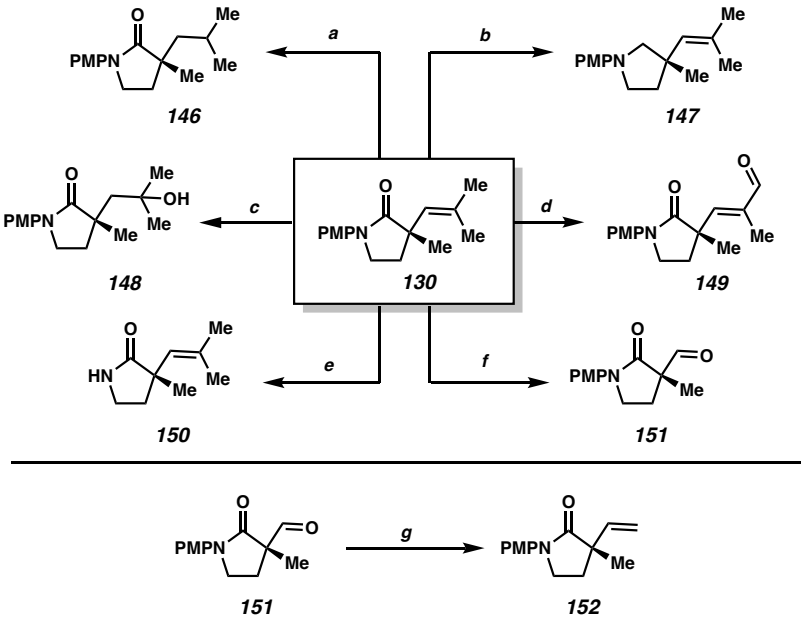
2.5 PRODUCT DERIVATIZATIONS

These enantioenriched heterocycles, adorned with highly substituted quaternary centers, exhibit significant potential for pharmaceutical and total synthetic applications.[7] As a result, we embarked on a series of derivatizations of product **130** to generate differentially substituted pyrrolidinone derivatives (Scheme 2.2). Our initial strategy involved the hydrogenation of product **130** to yield α-quaternary lactam **146**. Given the inherent challenges associated with enantioselective α-alkylation of lactams using conventional methods, we postulate that this alternative approach offers great synthetic value.

Reduction of the lactam with lithium aluminum hydride yielded β-quaternary pyrrolidine **147**. This derivative contains a heterocycle of significant pharmaceutical importance,[8] as pyrrolidines are ubiquitous in various existing drug molecules and natural

products.[9] Hydration of the vinyl group with *p*-TsOH produces tertiary alcohol **148**.[10] Allylic oxidation with SeO_2 results in the formation of aldehyde **149**. Additionally, the deprotection of the PMP group with ceric ammonium nitrate (CAN) reveals unprotected lactam **150**. Finally, **130** can undergo oxidative cleavage to yield the corresponding aldehyde **151** through ozonolysis. From **151**, a Wittig reaction can be conducted to generate vinylated lactam **152** with no substitution at the terminal position.[11]

Scheme 2.2 *Product derivatizations.*



[a] H_2, Pd/C (10 mol%), MeOH, 12h, 74 % yield. [b] LAH (5 equiv), Et_2O, 0–18 °C, 21 h, 84 % yield. [c] PTSA, AcOH, 70 °C, 12h, 59 % yield. [d] SeO_2, 1,4-dioxane, reflux, 15 min, 49% yield. [e] CAN, H_2O, 60 ºC, 32h, 40% yield. [f] O_3, PPh_3 CH_2Cl_2, 15min, 89% yield. [g] KO*t*-Bu, methyltriphenylphosphonium bromide, THF, 0 ºC to reflux, 12h, 84% yield.

2.6 CONCLUSIONS

In conclusion, our study showcases an enantioselective vinylation method for γ-lactams yielding α-quaternary centers in up to 58% yield and 94% ee. Notably, the reaction exhibits distinct preferences among different classes of electrophiles. Particularly, we observed that trisubstituted vinyl chlorides outperformed other vinyl halides under these

conditions in terms of both yield and ee. Moreover, these highly substituted γ-lactams hold significant synthetic potential, offering diverse functional handles for the synthesis of complex drug molecules or natural products.

2.7 EXPERIMENTAL SECTION

2.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[12] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz, Bruker 400 MHz, or Varian Mercury 300 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometer (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited

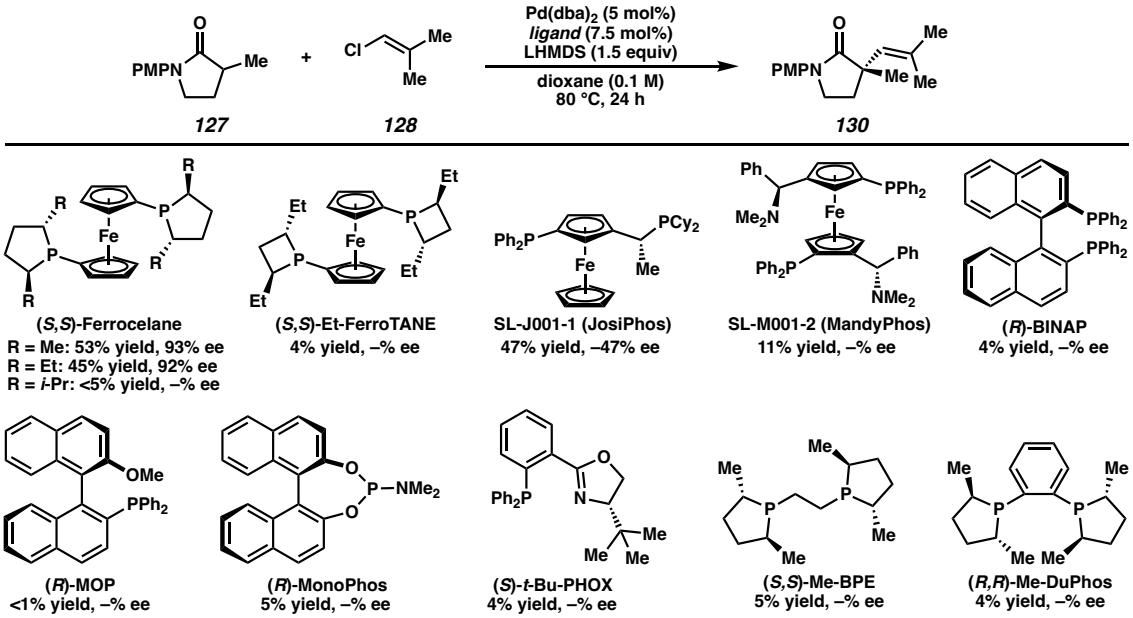
on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESIAPCI+), or obtained from Caltech mass spectrometry laboratory. Reagents were purchased from commercial sources and used as received unless otherwise stated.

2.7.1.1 Preparation of Known Compounds

Compound **127** was prepared according to a literature procedure,[3] and **128** and **129** were purchased from Sigma Aldrich.

2.7.2 ADDITONAL OPTIMIZATION DATA

Table 2.3 *Ligand evaluation.*[a]

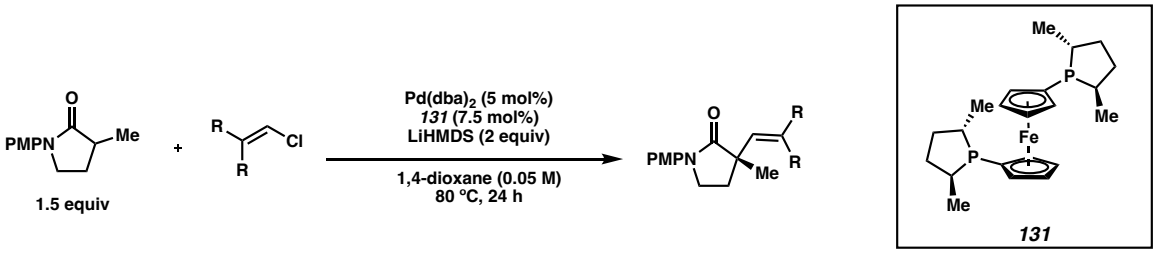


[a] Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. Enantiomeric excess (ee) was determined by chiral SFC analysis of the isolated product.

2.7.3 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

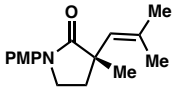
2.7.3.1 Pd-Catalyzed Vinylation Reactions

Preparation of α-Vinyl Lactams: General Procedure A



In a nitrogen-filled glovebox, a catalyst solution of $Pd(dba)_2$ (9.6 mg/mL) and **131** (10.4 mg/mL) in 1,4-dioxane was stirred for 20 min at 40 °C. In a vial, the lactam was dissolved in 1,4-dioxane (1.5 equiv, 0.09 M), and subsequently LHMDS (2.0 equiv) was

added. A 2-dram vial was charged with neat vinyl chloride (0.1 mmol, 1.0 equiv) and a magnetic stir bar. After the catalyst pre-stir was complete, 0.4 mL of the catalyst solution was added to the vinyl chloride, followed by 1.6 mL of the nucleophile/base mixture. The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 80 °C in a metal heating block for 24 h unless noted otherwise. After 24 h, 3 mL 0.5 M HCl or sat. NH_4Cl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography to provide the desired vinylation product.



130

***(S)*-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (130)**

Prepared according to general procedure A using vinyl chloride **128** (0.1 mmol) and lactam **127**. Purification by silica gel chromatography (0-30% EtOAc/Hexanes) provided 15 mg (58%, 94% ee) of a yellow oil. The reaction was also performed using 3 mmol vinyl chloride to obtain 456 mg (59%, 94% ee) of a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.46 (t, *J* = 1.4 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.63 (m, 2H), 2.32 – 2.12 (m, 2H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.36 (s, 3H).

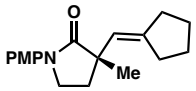
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.8, 156.5, 134.6, 133.3, 128.5, 121.6, 114.1, 55.6, 46.3, 45.7, 34.3, 27.1, 24.4, 19.2.

IR (Neat Film, NaCl): 2965, 1694, 1513, 1400, 1297, 1250, 1170, 1089, 1063, 1033, 828 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found 260.1649.

Optical rotation: $[\alpha]_D^{25}$ –79.9 (*c* 1.0, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, t_R (min): minor = 3.37, major = 5.18.



133

(*S*)-3-(cyclopentylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (133)

Prepared according to general procedure A using **155**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **133** as a white solid (15.6 mg, 55% yield, 90% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.53 (p, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.75 – 3.51 (m, 2H), 2.26 (m, 5H), 2.15 – 1.87 (m, 1H), 1.88 – 1.60 (m, 2H), 1.60 – 1.42 (m, 2H), 1.35 (s, 3H).

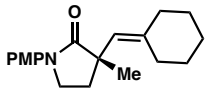
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.5, 145.1, 133.3, 123.7, 121.5, 114.1, 55.6, 47.1, 45.8, 35.5, 34.0, 28.9, 27.3, 25.8, 23.9.

IR (neat film, NaCl): 3835, 3732, 2951, 2866, 2360, 1693, 1511, 1455, 1395, 1298, 1248, 1181, 1084, 1035, 833, 662 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found 286.1815.

Optical rotation: $[\alpha]_D^{25}$ –56.8 (c 0.75, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 4.69, major = 7.78.



134

(*S*)-3-(cyclohexylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (134)

Prepared according to general procedure A using **156**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **134** as a white solid (15.3 mg, 51% yield, 84% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 5.36 – 5.31 (m, 1H), 3.69 (s, 3H), 3.67 – 3.34 (m, 2H), 2.12 (m, 2H), 2.08 – 1.94 (m, 4H), 1.55 – 1.32 (m, 6H), 1.25 (s, 3H).

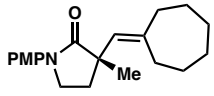
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 156.4, 142.7, 133.2, 125.4, 121.5, 114.0, 55.5, 45.9, 45.6, 37.7, 34.6, 30.2, 28.7, 27.6, 26.5, 24.7.

IR (neat film, NaCl): 3835, 3745, 2925, 2851, 2359, 1693, 1513, 1443, 1396, 1298, 1248, 1179, 1088, 1035, 828 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{19}H_{26}NO_2$ $[M+H]^+$: 300.1958, found 300.1972.

Optical rotation: $[\alpha]_D^{25}$ –64.5 (c 1.0, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.21, major = 9.35.



135

(*S*)-3-(cycloheptylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (135)

Prepared according to general procedure A using **157**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **135** as a white solid (4.7 mg, 15% yield, 86% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.52 (p, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.32 (m, 2H), 2.86 – 1.98 (m, 6H), 1.84 – 1.40 (m, 8H), 1.36 (s, 3H).

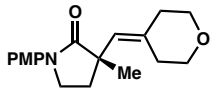
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 156.5, 144.2, 133.3, 128.8, 121.6, 121.6, 114.2, 55.6, 46.3, 45.8, 38.5, 34.1, 31.0, 29.9, 29.7, 29.3, 27.0, 24.4.

IR (neat film, NaCl): 3834, 3732, 2923, 2849, 2341, 1693, 1511, 1395, 1298, 1247, 1087, 1035, 827 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{20}H_{28}NO_2$ $[M+H]^+$: 314.2115, found 314.2029.

Optical rotation: $[\alpha]_D^{25}$ – 39.4 (c 0.5, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.32, major = 9.13.



136

(*S*)-3-(tetrahydropyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (136)

Prepared according to general procedure A using **158**. Purification by column chromatography (0–30% EtOAc/Hexanes) yielded **136** as a colorless oil (13.2 mg, 43%, 88% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.57 (m, 6H), 2.34 (tt, *J* = 5.8, 1.2 Hz, 2H), 2.29 – 2.17 (m, 4H), 1.37 (s, 3H).

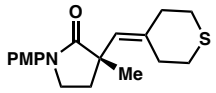
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.6, 137.5, 133.1, 127.5, 121.6, 114.2, 69.8, 68.4, 55.6, 46.0, 45.7, 37.5, 34.9, 31.3, 24.8.

IR (neat film, NaCl): 2958, 2839, 1691, 1511, 1462, 1396, 1286, 1269, 1246, 1087, 1032, 831 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1750.

Optical rotation: $[\alpha]_D^{25}$ – 41.4 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 8.03, major = 11.15.



137

(*S*)-3-(tetrahydro-thiopyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (137)

Prepared according to general procedure A using **159**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **137** as a colorless oil (13.5 mg, 44%, 86% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 9.1 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 5.55 (t, *J* = 1.0 Hz, 1H), 3.80 (s, 2H), 3.78 – 3.68 (m, 1H), 2.76 – 2.48 (m, 4H), 2.44 (td, *J* = 5.4, 2.5 Hz, 1H), 2.24 – 2.17 (m, 1H), 1.36 (s, 2H).

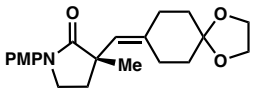
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.6, 139.6, 133.05, 129.0, 121.6, 114.2, 55.6, 45.9, 45.7, 39.4, 34.8, 32.2, 31.2, 29.9, 24.8.

IR (neat film, NaCl): 2953, 1689, 1511, 1428, 1398, 1297, 1247, 1180, 1087, 1034, 821 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_{18}H_{24}NO_2S$ $[M+H]^+$: 318.1522, found 318.1520.

Optical rotation: $[\alpha]_D^{25}$ –58.3 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OJ-3 column, λ = 254 nm, tR (min): minor = 7.45, major = 6.32.



138

(*S*)-3-((1,4-dioxaspiro[4.5]decan-8-ylidene)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (138)

Prepared according to general procedure A using **160**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **138** (48% yield, 74% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.7 Hz, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 3.76 – 3.60 (m, 2H), 2.40 – 2.29 (m, 2H), 2.31 – 2.16 (m, 4H), 1.71 (td, *J* = 6.7, 3.9 Hz, 3H), 1.68 – 1.62 (m, 1H), 1.60 (s, 1H), 1.37 (s, 3H).

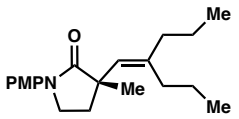
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.7, 156.6, 140.0, 133.2, 127.2, 121.6, 114.2, 114.1, 108.7, 77.5, 77.4, 77.2, 76.8, 64.5, 64.5, 55.6, 46.1, 45.7, 36.4, 35.3, 34.7, 34.5, 26.7, 24.7.

IR (thin film, NaCl): 3465, 2950, 2886, 2320, 2009, 1902, 1693, 1681, 1513, 1433, 1401, 1298, 1276, 1248, 1226, 1181, 1171, 1120, 1082, 1032, 944, 906, 826, 738, 728 cm^{-1}.

HRMS (ESI): m/z calc'd $C_{21}H_{27}NO_4Na$ $[M+Na]^+$: 380.1832, found: 380.1843.

Optical rotation: $[a]_D^{25}$ + 4.5 ° (*c* 0.52, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.53, major = 5.02.



139

(S)-1-(4-methoxyphenyl)-3-methyl-3-(2-propylpent-1-en-1-yl)pyrrolidin-2-one (139)

Prepared according to general procedure A using **161**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **139** (58% yield, 92% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.50 (t, *J* = 1.0 Hz, 1H), 3.80 (d, *J* = 0.7 Hz, 3H), 3.78 – 3.67 (m, 2H), 2.34 – 2.25 (m, 1H), 2.25 – 2.17 (m, 1H), 2.12 – 2.03 (m, 1H), 2.03 – 1.94 (m, 3H), 1.48 – 1.38 (m, 4H), 1.36 (s, 3H), 0.93 – 0.84 (m, 6H).

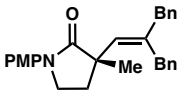
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 156.4, 142.4, 133.2, 128.5, 121.4, 114.0, 77.4, 77.2, 77.0, 76.7, 55.5, 46.2, 45.6, 38.8, 34.5, 33.0, 24.7, 21.3, 21.1, 14.6, 13.8.

IR (thin film, NaCl): 2958, 2930, 2870, 1694, 1513, 1469, 1454, 1423, 1398, 1299, 1288, 1248, 1181, 1168, 1122, 1087, 1036, 836, 823, 805, 634 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{20}H_{29}NO_2Na$ $[M+Na]^+$: 338.2091, found: 338.2100.

Optical rotation: $[a]_D^{25}$ – 2.5 ° (*c* 0.35, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 2.88, major = 3.73.



140

(S)-3-(2-benzyl-3-phenylprop-1-en-1-yl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (140)

Prepared according to general procedure A using **162**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **140** (22% yield, 88% ee) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 9.1 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 7.17 – 7.10 (m, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 6.02 (t, *J* = 1.0 Hz, 1H), 3.86 (s, 3H), 3.84 – 3.74 (m, 2H), 3.54 – 3.38 (m, 2H), 3.27 (t, *J* = 1.6 Hz, 2H), 2.43 (dt, *J* = 12.5, 8.2 Hz, 1H), 2.30 (ddd, *J* = 12.5, 7.2, 3.6 Hz, 1H), 1.52 (s, 3H).

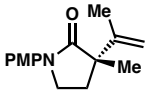
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 156.5, 139.8, 139.5, 139.0, 132.9, 132.8, 129.0, 128.9, 128.5, 128.3, 128.2, 126.1, 121.6, 114.1, 77.4, 77.2, 77.0, 76.7, 55.5, 46.4, 45.7, 43.3, 35.9, 34.1, 24.8.

IR (thin film, NaCl): 3059, 3025, 2930, 2835,m 2340, 1682, 1600, 1520, 1493, 1453, 1398, 1298, 1240, 1181, 1120, 1088, 1031, 829, 734, 702 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{28}H_{29}NO_2Na$ $[M+Na]^+$: 434.2091, found: 434.2102.

Optical rotation: $[a]_D^{25}$ – 12.4 ° (*c* 0.56, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.63, major = 7.11.



143

(S)-1-(4-methoxyphenyl)-3-methyl-3-(prop-1-en-2-yl)pyrrolidin-2-one (143)

Prepared according to general procedure A using **142**. The crude product was purified by silica gel chromatography (0–30% EtOAc/Hexanes) to afford vinylated lactam **143** (8.3 mg, 34% yield, 92% ee) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.93 (s, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.76 – 3.44 (m, 2H), 2.32 (ddd, *J* = 12.7, 7.0, 4.4 Hz, 1H), 1.94 (dt, *J* = 12.7, 7.8 Hz, 1H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.39 (s, 3H).

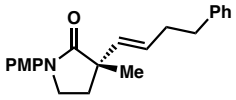
^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 156.6, 145.4, 133.1, 121.7, 114.2, 114.1, 111.9, 55.6, 51.2, 45.9, 31.9, 22.5, 19.8.

IR (thin film, NaCl): 2933, 1738, 1693, 1643, 1512, 1455, 1396, 1297, 1248, 1181, 1088, 1034, 892, 828 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1498, found 246.1495.

Optical rotation: $[a]_D^{25}$ – 125.8 ° (*c* 1, $CHCl_3$).

SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.77, major = 4.09.



145

(S,E)-1-(4-methoxyphenyl)-3-methyl-3-(4-phenylbut-1-en-1-yl)pyrrolidin-2-one (145)

Prepared according to general procedure A using **144**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **145** (20.6 mg, 62% yield, 19% ee) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 – 7.38 (m, 2H), 7.22 – 7.12 (m, 2H), 7.12 – 6.99 (m, 3H), 6.89 – 6.73 (m, 2H), 5.57 – 5.38 (m, 2H), 3.72 (s, 3H), 3.63 – 3.49 (m, 2H), 2.66 –

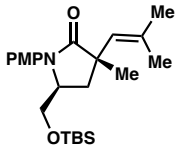
2.53 (m, 2H), 2.35 – 2.19 (m, 2H), 2.07 (ddd, J = 12.4, 6.3, 5.0 Hz, 1H), 1.89 (dt, J = 12.5, 7.7 Hz, 1H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 156.5, 141.9, 133.1, 133.1, 129.0, 128.7, 128.4, 125.9, 121.5, 114.1, 55.6, 47.8, 45.6, 35.9, 34.5, 32.7, 23.6.

IR (thin film, NaCl): 2928, 1693, 1513, 1461, 1395, 1297, 1249, 1181, 1091, 1032, 974, 830, 798, 739, 700 cm^{-1}.

HRMS (FD+): m/z calc'd $C_{22}H_{25}NO_2$ $[M]^{+\bullet}$, 335.1885, found 335.1890.

SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 254 nm, tR (min): minor = 7.77, major = 9.64.



141

(3S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (141)

Prepared according to general procedure A using **128**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **141** (21 mg, 52% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 6.92 – 6.86 (m, 2H), 5.41 (h, *J* = 1.4 Hz, 1H), 4.09 (dddd, *J* = 8.6, 5.8, 4.4, 2.8 Hz, 1H), 3.80 (s, 3H), 3.62 – 3.45 (m, 2H), 2.41 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.13 (dd, *J* = 12.9, 5.7 Hz, 1H), 1.70 (dd, *J* = 3.6, 1.4 Hz, 6H), 1.47 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), -0.09 (d, *J* = 13.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.9, 157.8, 134.1, 130.7, 129.8, 126.5, 114.3, 62.6, 58.5, 55.6, 45.3, 37.5, 27.1, 27.0, 26.0, 19.1, 18.4, 1.2, -5.5, -5.5.

IR (thin film, NaCl): 2932, 2857, 1693, 1513, 1467, 1401, 1247, 1104, 1043, 826 cm^{-1}.

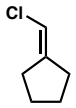
HRMS (MM:ESI-APCI+): m/z calc'd $C_{23}H_{38}NO_3Si$ $[M+H]^+$: 404.2615, found 404.2626.

Optical rotation: $[a]_D^{25}$ – 36.8 ° (*c* 1, $CHCl_3$).

2.7.3.2 Preparation of Vinyl Chloride Starting Materials

Preparation of Vinyl Chloride Substrates: General Procedure B

To a stirred suspension of (chloromethyl)triphenylphosphonium chloride (2.60 g, 7.50 mmol, 1.5 equiv) in diethyl ether (60 mL) was added sodium bis(hexamethylsilyl)amide (1.38 g, 7.50 mmol, 1.5 equiv) in diethyl ether (15 mL) at –78 °C or 0 ºC, and the resulting mixture was stirred at this temperature for 1 h. Then, ketone (5 mmol, 1.0 equiv) was added dropwise, and the reaction was allowed to slowly warm to room temperature and stirred overnight. After 18 h, the reaction was quenched with water (50 mL), transferred to a separatory funnel, and extracted with diethyl ether (20 mL) three times. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired vinyl chloride.



155

(chloromethylene)cyclopentane (155)

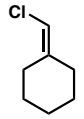
Prepared according to general procedure B using cyclopentanone. Purification by column chromatography (100% Hexanes) yielded **155** as a clear oil (209 mg, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (p, *J* = 2.4 Hz, 1H), 2.42 – 2.23 (m, 4H), 1.80 – 1.63 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.9, 108.0, 32.6, 30.7, 27.4, 25.8.

IR (neat film, NaCl): 3817, 3645, 2955, 2359, 1650, 1455, 772, 653 cm^{-1}.

HRMS (FI+): m/z calc'd for C_6H_9Cl $[M]^{+\bullet}$: 116.0400, found 116.0393.



156

(chloromethylene)cyclohexane (156)

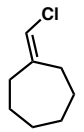
Prepared according to general procedure B using cyclohexanone. Purification by silica gel chromatography (100% Hexanes) yielded **156** as a clear oil (419 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (p, J = 1.2 Hz, 1H), 2.32 (m, 2H), 2.13 (m, 2H), 1.55 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.3, 108.5, 34.2, 28.6, 28.0, 26.8, 26.5.

IR (neat film, NaCl): 3817, 3732, 3064, 2937, 2356, 1636, 1541, 1455, 1336, 1293, 1231, 986, 786 cm^{-1}.

HRMS (FI+): m/z calc'd for $C_7H_{11}Cl$ $[M]^{+\bullet}$: 130.0549, found 130.0558.



157

(chloromethylene)cycloheptane (157)

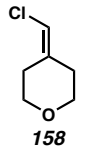
Prepared according to general procedure B using cycloheptanone. Purification by silica gel chromatography (100% Hexanes) yielded **157** as a colorless oil (557 mg, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (p, *J* = 1.5 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.30 – 2.22 (m, 2H), 1.70 – 1.55 (m, 4H), 1.53 – 1.43 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.7, 111.7, 35.2, 30.9, 30.2, 29.4, 29.0, 26.2.

IR (neat film, NaCl): 3380, 2921, 2859, 2360, 1674, 1506, 1069, 682 cm^{-1}.

HRMS (FI+): m/z calc'd for $C_8H_{13}Cl$ $[M]^{+\bullet}$: 144.0712, found 144.0706.



158

4-(chloromethylene)tetrahydro-2H-pyran (158)

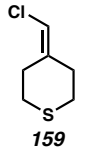
Prepared according to general procedure B using tetrahydro-4*H*-pyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **158** (136 mg, 45%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (t, *J* = 1.3 Hz, 1H), 3.69 (dt, *J* = 7.5, 5.5 Hz, 4H), 2.46 (ddd, *J* = 6.5, 5.3, 1.3 Hz, 2H), 2.27 (ddd, *J* = 6.2, 5.0, 1.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2, 110.6, 68.8, 68.0, 34.3, 29.5.

IR (thin film, NaCl): 3069, 2961, 2907, 2848, 2747, 2704, 2360, 1954, 1645, 1466, 1432, 1380, 1356, 1323, 1296, 1228, 1165, 1099, 1021, 1000, 923, 859, 822, 792, 749 cm^{-1}.

HRMS (FI+): m/z calc'd for C_6H_9ClO $[M]^{+\bullet}$: 132.0342, found 132.0348.



159

4-(chloromethylene)tetrahydro-2H-thiopyran (159)

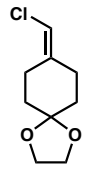
Prepared according to general procedure B using tetrahydro-4*H*-thiopyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **159** (189 mg, 81%) as a colorless, malodorous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (d, *J* = 1.1 Hz, 1H), 2.71 – 2.62 (m, 6H), 2.51 – 2.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.3, 111.7, 36.0, 30.5, 30.4, 29.4.

IR (thin film, NaCl): 3065, 2949, 2907, 2829, 2360, 1649, 1626, 1425, 1337, 1323, 1291, 1270, 1223, 1171, 991, 975, 938, 822, 797 cm^{-1}.

HRMS (FI+): m/z calc'd for C_6H_9ClS $[M]^{+\bullet}$: 148.0114, found 148.0123.



160

8-(chloromethylene)-1,4-dioxaspiro[4.5]decane (160)

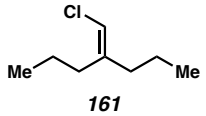
Prepared according to general procedure B using 1,4-dioxaspiro[4.5]decan-8-one. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **160** (79% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (d, *J* = 1.4 Hz, 1H), 3.97 (s, 4H), 2.53 – 2.43 (m, 2H), 2.30 (td, *J* = 6.5, 1.3 Hz, 2H), 1.76 – 1.63 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.6, 110.0, 108.6, 77.5, 77.2, 76.8, 64.6, 35.6, 34.5, 30.9, 25.4.

IR (thin film, NaCl): 3068, 2950, 2930, 2883, 2685, 2728, 2685, 1718, 1654, 1634, 1443, 1366, 1341, 1295, 1272, 1246, 1225, 1186, 1100, 1080, 1034, 962, 943, 908, 828, 797, 770., 748, 678 cm^{-1}.

HRMS (FI+): m/z calc'd $C_9H_{13}ClO_2$ $[M]^{+\bullet}$: 188.0604, found: 188.0619.



161

4-(chloromethylene)heptane (161)

Prepared according to general procedure B using 4-heptanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **161** (27% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 – 5.73 (m, 1H), 2.21 – 2.14 (m, 2H), 2.03 (td, *J* = 7.6, 1.3 Hz, 2H), 1.58 – 1.34 (m, 4H), 0.91 (dt, *J* = 16.5, 7.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.7, 112.1, 77.5, 77.2, 76.8, 37.0, 32.2, 21.0, 20.5, 14.1, 13.9.

IR (thin film, NaCl): 3066, 2980, 2933, 2872, 1911, 1630, 1465, 1456, 1379, 1319, 1169, 1109, 836, 791, 766 cm^{-1}.

HRMS (FI+): m/z calc'd $C_8H_{15}Cl$ $[M]^{+\bullet}$: 146.0862, found: 146.0872.

162

(2-(chloromethylene)propane-1,3-diyl)dibenzene (162)

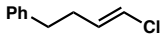
Prepared according to general procedure B using 1,3-diphenyl-2-propanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **162** (68% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 7.27 – 7.23 (m, 2H), 7.19 – 7.14 (m, 2H), 6.07 – 6.01 (m, 1H), 3.56 (s, 2H), 3.32 (d, *J* = 1.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 138.3, 138.0, 129.1, 128.9, 128.6, 128.5, 126.6, 126.4, 114.9, 77.4, 77.0, 76.7, 40.4, 35.6.

IR (thin film, NaCl): 3088, 3062, 3020, 2916, 2845, 2355, 1947, 1872, 1809, 1633, 1601, 1494, 1453, 1433, 1310, 1296, 1178, 1075, 1029, 960, 906, 870, 829,787, 740, 703, 634 cm^{-1}.

HRMS (FI+): m/z calc'd $C_{16}H_{15}Cl$ $[M]^{+\bullet}$: 242.0862, found: 242.0889.



144

(*E*)-(4-chlorobut-3-en-1-yl)benzene (144)

Inspired by a literature protocol, 4-phenyl-1-butyne (523 mg, 4.02 mmol) was dissolved in hexanes (1 M) in a two-neck flask. Under a N_2 atmosphere, neat DIBAL-H (0.788 mL, 1.1 equiv) was added slowly at ambient temperature. The reaction was heated to 50ºC for 2.5 h before being slowly chilled to 18 ºC, at which point Et_2O (2 M) was added. At –78ºC, solid NCS (1.08 g, 2 equiv) was quickly added through one neck of the flask. The reaction was allowed to warm to 18 ºC. After 16h, the reaction mixture was poured into a flask containing 30 mL pentane and 15 mL 6 M HCl with ice. The organic layer was extracted with Et_2O three times, after which it was washed with 10 mL 1 M NaOH then sat. $Na_2S_2O_3$ (10 mL). The organic layer was then dried with Na_2SO_4, filtered, and concentrated, at which point purification by silica gel chromatography (100% Hexanes) yielded the desired vinyl chloride **144** (205 mg, 25% yield).

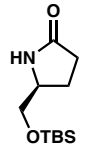
Characterization data in agreement with the literature.[13]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, J = 8.0, 6.8 Hz, 2H), 7.23 – 7.14 (m, 3H), 6.07 – 5.79 (m, 2H), 2.71 (dd, J = 8.7, 6.7 Hz, 2H), 2.45 – 2.26 (m, 2H).

2.7.3.3 Preparation of New Lactam Starting Materials

Following a literature protocol, enantiopure 5-(hydroxymethyl)pyrrolidin-2-one was dissolved in CH_2Cl_2 (0.86 M). Iteratively, TBSCl (1.2 equiv) and imidazole (1.5 equiv) were added. The reaction was stirred for 4h, after which it was quenched with H_2O and separated into layers. The aqueous phase was extracted with CH_2Cl_2 two more times, and

the combined organic extracts were dried with Na_2SO_4. The product was isolated as a colorless oil (quant.) and used in the next step without additional purification.

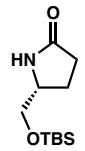


163

(*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one (163)

Prepared according to a literature procedure. Characterization data was in agreement with the literature.[14]

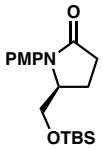
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (s, 1H), 3.92 – 3.70 (m, 1H), 3.63 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.44 (dd, *J* = 10.1, 7.9 Hz, 1H), 2.35 (ddd, *J* = 8.6, 7.2, 2.8 Hz, 2H), 2.25 – 2.09 (m, 1H), 1.73 (dddd, *J* = 13.2, 9.3, 7.7, 5.5 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).



164

(*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one (164)

Refer to **163** for ^{1}H NMR data.



165

(*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (165)

In a flask equipped with a magnetic stir bar, CuI (0.5 mmol, 10 mol%) was combined with anhydrous K_2CO_3 (10 mmol, 2 equiv). The vial was purged and backfilled with N_2 three times. At this point, 5 mL of toluene was added, followed by N, N'-

dimethylethylenediamine (1 mmol, 20 mol%), intermediate **165** or **166** (6 mmol, 1.2 equiv), and p-Br anisole (5 mmol). The reaction mixture was allowed to react at 100 ºC for 24h. The crude reaction mixture was concentrated and purified by silica gel chromatography (0-100% EtOAc/Hexanes) to afford the product as a yellow oil (1.10 g, 66% yield).

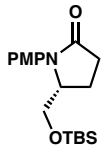
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.12 (dtd, *J* = 8.6, 3.6, 2.5 Hz, 1H), 3.80 (3, 2H), 3.68 – 3.43 (m, 2H), 2.68 (ddd, *J* = 16.9, 10.1, 8.1 Hz, 1H), 2.49 (ddd, *J* = 16.9, 10.2, 4.6 Hz, 1H), 2.26 (ddt, *J* = 12.8, 10.1, 8.3 Hz, 1H), 2.09 (dddd, *J* = 12.7, 10.1, 4.6, 3.5 Hz, 1H), 0.86 (s, 9H), -0.04 (d, *J* = 11.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 157.9, 130.5, 126.5, 114.5, 63.0, 62.0, 55.6, 31.6, 25.9, 21.5, 18.3, -5.47, -5.51.

IR (thin film, NaCl): 2934, 1694, 1513, 1248, 1090, 834, 682 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{18}H_{30}NO_3Si$ $[M+H]^+$: 336.1989, found 336.1999.

Optical rotation: $[\alpha]_D^{25}$ –48.0º (c 1.0, $CHCl_3$).

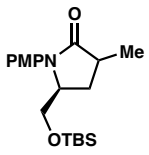


166

(*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (166)

Refer to Compound **165** for ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.

Optical rotation: $[\alpha]_D^{25}$ 47.9º (c 1.0, $CHCl_3$).



167

(*5S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (167)

A solution of LDA was prepared by the slow addition of n-BuLi (1.44 mL, 2.5 M in hexanes) to a solution of diisopropylamine (3.61 mmol) in THF (0.9 M) at -78ºC. After letting the mixture stir for 1h at this temperature, substrate **165** or **166** was added slowly as a solution in THF (0.3 M). 30 min later, MeI (3.61 mmol) was added slowly to the reaction mixture, and it was allowed to warm up to 18 ºC. After 16h, the reaction was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The crude compound was concentrated and purified by silica gel chromatography (10-60% EtOAc/Hexanes) to afford the product as a dark solid (703 mg, 61% yield).

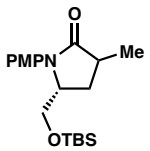
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.15 – 4.01 (m, 1H), 3.81 (s, 3H), 3.68 – 3.43 (m, 2H), 2.81 (td, *J* = 9.1, 7.1 Hz, 1H), 2.33 (ddd, *J* = 12.7, 9.0, 2.0 Hz, 1H), 1.90 (dt, *J* = 12.6, 9.1 Hz, 1H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), -0.03 (d, *J* = 11.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.5, 157.5, 131.0, 125.7, 114.4, 63.0, 59.9, 55.6, 36.8, 30.9, 25.9, 18.3, 17.1, -5.45, -5.48.

IR (thin film, NaCl): 2928, 1693, 1513, 1463, 1272, 1246, 1171, 1107, 1041, 832, 776, 681 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{19}H_{32}NO_3Si$ $[M+H]^+$: 350.2146, found 350.2143.

Optical rotation: $[\alpha]_D^{25}$ –30.0º (c 1.0, $CHCl_3$).



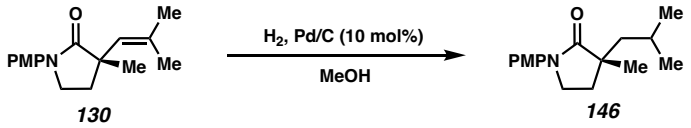
153

(*5R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (153)

Refer to Compound **167** for ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.

Optical rotation: $[\alpha]_D^{25}$ 32.3º (c 1.0, $CHCl_3$).

2.7.2.4 Derivatization of Lactam Products



130 *146*

(*R*)-3-isobutyl-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (146)

A flamed-dried one-dram vial was charged with a stir bar and starting material **130** (15 mg, 0.058mmol, 1 equiv) in MeOH (0.421uL, 0.1M), followed by Pd/C (10%) (6.23mg, 0.058 mmol, 1 equiv). Reaction mixture was purged with N_2 for 5 minutes and then with H_2, and the mixture was stirred overnight with a H_2 balloon. Upon complete consumption of starting material as determined by TLC (30% EtOAc in Hexanes), the reaction was quenched by filtering through a pad of celite with DCM. The filtrate was concentrated in vacuo, and the crude product was purified by prep TLC (25% EtOAc/Hexanes) to afford lactam **146** (7.6 mg, 74% yield) as a pale yellow oil.

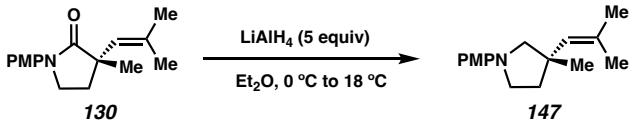
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.44 (m, 2H), 7.04 – 6.81 (m, 2H), 3.80 (s, 3H), 3.77 – 3.65 (m, 2H), 2.17 (ddd, *J* = 12.7, 8.4, 7.0 Hz, 1H), 1.92 (ddd, *J* = 12.6, 7.8, 4.7 Hz, 1H), 1.79 (dqd, *J* = 8.3, 6.6, 4.6 Hz, 1H), 1.68 – 1.58 (m, 2H), 1.49 (dd, *J* = 14.1, 8.3 Hz, 1H), 1.21 (s, 3H), 0.94 (dd, *J* = 17.5, 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.6, 156.5, 133.3, 121.6, 114.1, 55.6, 46.2, 45.7, 45.2, 31.3, 25.2, 25.0, 23.8, 23.4.

IR (thin film, NaCl): 3358, 2953, 2930, 2869, 2837, 2058, 1885, 1700, 1610, 1518, 1461, 1453, 1394, 1366, 1313, 1290, 1252, 1233, 1184, 1168, 1121, 1036, 1011, 830, 805, 743, 722.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{23}NO_2Na$ $[M+Na]^+$: 284.1621, found: 284.1628.

Optical rotation: $[\alpha]_D^{25}$ – 117.2 ° (*c* 0.20, $CHCl_3$).



130 *147*

(*S*)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidine (147)

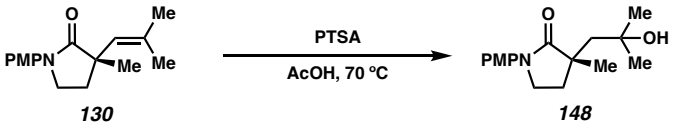
Following our previous report,[15] solid LAH was added to a solution of lactam **130** in Et_2O (0.1 M) at 0 ºC. The solution was stirred at this temperature for 5 min and then was allowed to warm to 18 ºC. After 21 h, the reaction was quenched with H_2O. Extractions were performed with EtOAc seven times, and the crude product was subjected to silica gel chromatography (0-40% EtOAc/Hexanes) to afford the desired product (**147**) as a white solid (22.5 mg, 84% yield).

^{1}H NMR (400 MHz, CDCl3): δ 6.85 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 5.34 (s, 1H), 3.76 (s, 3H), 3.35 – 3.13 (m, 4H), 2.10 – 2.00 (m, 1H), 1.92 (s, 1H), 1.73 (d, J = 1.3 Hz, 3H), 1.70 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, CDCl3): δ 132.7, 132.0, 115.2, 112.14, 61.46, 56.24, 47.11, 42.40, 39.67, 27.21, 25.77, 19.41.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{24}NO$ $[M+H]^+$: 245.1780, found 245.1784.

Optical rotation: $[a]_D^{25}$ 5.5° (*c* 1.0, $CHCl_3$).



130 *148*

(*S*)-3-(2-hydroxy-2-methylpropyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (148)

In a one-dram vial, starting material **130** (10.9mg, 0.042 mmol, 1 equiv) was combined with PTSA (4mg, 0.021 mmol, 0.5 equiv) and acetic acid (700uL, 0.06M). The reaction mixture was heated to 70 ºC overnight, and reaction was tracked by LCMS. After completion, saturated aqueous $NaHCO_3$ was added to quench the reaction, and then extracted with DCM and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified via prep TLC (50% EtOAc/Hexanes) to afford alcohol **148** (6.3 mg, 59% yield) as a colorless oil.

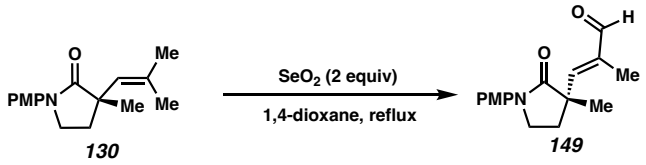
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.22 (ddd, *J* = 12.1, 8.7, 5.3 Hz, 1H), 3.12 (ddd, *J* = 12.1, 8.8, 6.7 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.07 – 1.78 (m, 3H), 1.47 (s, 3H), 1.39 (d, *J* = 5.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.6, 152.5, 142.3, 115.0, 114.4, 81.3, 77.5, 77.4, 77.2, 76.8, 55.9, 46.4, 44.1, 41.0, 38.7, 30.4, 30.2, 26.6.

IR (thin film, NaCl): 3369, 2968, 2930, 2834, 2339, 1754, 1681, 1513, 1455, 1401, 1377, 1265, 1249, 182, 1171, 1115, 1098, 1035, 942, 824.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1771.

Optical rotation: $[\alpha]_D^{25}$ 4.1950 ° (*c* 0.60, $CHCl_3$).



130 *149*

(*S,E*)-3-(1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidin-3-yl)-2-methylacrylaldehyde (149)

To a solution of **130** (26 mg, 0.1 mmol) in dioxane (0.2 M) was added SeO_2 (22 mg, 0.2 mmol), and the reaction was heated to reflux. After 15 minutes, starting material was consumed by TLC. The crude reaction was concentrated and passed through a silica plug (ca. 1" silica), eluting with 35% EtOAc/Hexanes, to afford the desired aldehyde **149** as a tan solid (13.4 mg 49% yield).

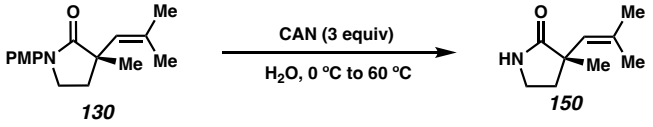
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 1.4 Hz, 1H), 3.88 (m, 1H), 3.81 (s, 4H), 3.78 – 3.35 (m, 1H), 2.43 – 2.31 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.8, 175.4, 157.0, 156.1, 139.7, 132.5, 121.8, 114.3, 55.6, 47.5, 45.8, 32.5, 22.9, 10.1.

IR (neat film, NaCl): 3834, 3732, 2958, 2359, 1688, 1512, 1396, 1299, 1249, 1178, 1090, 1031, 833 cm^{-1}.

HRMS (FI+): m/z calc'd for $C_{16}H_{19}NO_3$ $[M]^{+\bullet}$: 273.1365, found 273.1393.

Optical rotation: $[\alpha]_D^{25}$ –60.6º (c 1.0, $CHCl_3$).



130 *150*

(*S*)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (150)

A solution of CAN (82 mg, 0.15 mmol) in deionized H_2O (0.05 M) was added dropwise to a solution of **130** (26 mg, 0.1 mmol) at 0 °C, and the reaction was allowed to slowly warm to room temperature. After 12 hours, starting material remained by TLC. CAN (82 mg, 0.15 mmol) added, and the reaction was allowed to continue at 23 °C. After 2 h, the reaction

was heated to 60 °C and continued for 18 hours, at which point starting material was consumed by TLC. The reaction was cooled, diluted with ethyl acetate and water, transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate, the combined organics were dried with Na_2SO_4, filtered and concentrated. The material was purified with silica gel chromatography (5–10% MeOH/CH_2Cl_2) to afford the desired lactam **150** as a white solid (6.2 mg, 40% yield).

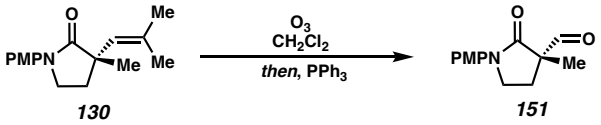
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 – 5.97 (bs, 1H), 5.38 (p, *J* = 1.4 Hz, 1H), 3.32 (ddd, *J* = 8.2, 5.5, 0.9 Hz, 2H), 2.39 – 1.87 (m, 2H), 1.72 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.8, 134.7, 128.1, 44.0, 39.0, 36.8, 27.0, 24.4, 19.1.

IR (neat film, NaCl): 3835, 3732, 3229, 2964, 2927, 2358, 1697, 1454, 1281, 1062, 832 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd for $C_9H_{16}NO$ $[M+H]^+$: 154.1226, found 154.1230.

Optical rotation: $[\alpha]_D^{25}$ –15.7 (c 0.5, $CHCl_3$).

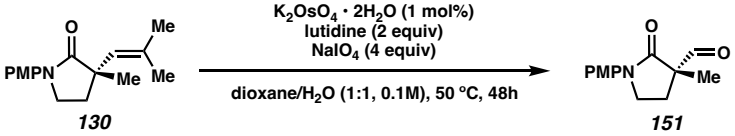


130 *151*

(*S*)-1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carbaldehyde (151)

Procedure A: A flamed-dried one-dram vial was charged with stir bar, and starting material **151** (50mg, 0.2 mmol, 1 equiv) was added with CH_2Cl_2 (482uL, 0.4M). The reaction mixture was cooled to – 78 ºC in a dry-ice bath, and ozone (1 atm) was bubbled through until all starting material was consumed as indicated by TLC. Then, O_2 gas was bubbled through to quench the residual ozone, and PPh_3 (101.2mg, 0.4 mmol, 2 equiv) was added and reaction was warmed to room temperature. The crude mixture was concentrated

in vacuo and purified by silica gel chromatography (30% EtOAc/Hexanes) to afford aldehyde **151** (40 mg, 89% yield) as a white solid.



Procedure B: A one-dram vial was charged with a stir bar and compound **130**. To this vial, 2,6-lutidine (2 equiv) and K_2OsO_4 • 2 H_2O was added as a solution in dioxane/H_2O. To the stirring mixture, NaIO4 was added and the temperature was increased to 50 ºC. After 24 h, the crude mixture was filtered through a pad of celite, eluting with CH_2Cl_2 and EtOAc. H_2O was added and CH_2Cl_2 was used to perform an extraction. The organic layer was washed with brine and dried with Na_2SO_4. The crude compound was purified via silica gel chromatography to afford compound **151**.[16]

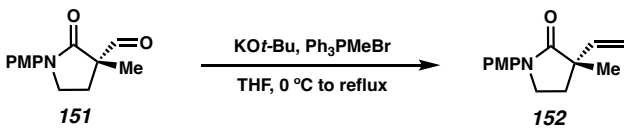
Optical rotation: $[a]_D^{25}$ – 26.8 ° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, *J* = 0.7 Hz, 1H), 7.56 – 7.43 (m, 2H), 6.96 – 6.83 (m, 2H), 3.93 – 3.67 (m, 5H), 2.75 (ddd, *J* = 12.9, 8.0, 4.8 Hz, 1H), 1.91 (dddd, *J* = 13.1, 8.6, 6.7, 0.7 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5, 171.3, 157.1, 132.2, 121.9, 114.3, 58.0, 55.6, 46.0, 25.9, 18.8.

IR (thin film, NaCl): 2932, 2358, 1731, 1682, 1520, 1455, 1402, 1297, 1248, 1170, 1092, 1032, 825 cm^{-1}.

HRMS (MM:ESI-APCI+): m/z calc'd $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125, found 234.1121.



(*S*)-1-(4-methoxyphenyl)-3-methyl-3-vinylpyrrolidin-2-one (152)

A one-dram vial was flame dried and charged with stir bar. The Ph_3PCH_2Br (51mg, 0.145mmol, 2.5 equiv) was added in THF (300uL, 0.1M) and cooled to 0 ºC. Reaction mixture was then charged with KO*t*-Bu (14mg, 0.128 mmol, 2.2 equiv) and stirred at 0 ºC for 20 minutes. Starting material **130** (13.2 mg, 0.057 mmol, 1 equiv) was added with the remaining THF (about 100 μL) and slowly warmed to room temperature and heated to reflux overnight. Second day all starting material was consumed by TLC (50% EtOAc/Hexanes) and reaction was quenched with NH_4Cl and extracted with EtOAc (3x) and washed with brine. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant crude product was the purified by pipette column chromatography (15% EtOAc/Hexanes) to afford vinylated lactam **152** (11 mg, 84% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.48 (m, 2H), 6.95 – 6.80 (m, 2H), 5.97 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.24 – 5.11 (m, 2H), 3.80 (s, 3H), 3.73 (ddt, *J* = 7.8, 5.0, 2.5 Hz, 2H), 2.26 (ddd, *J* = 12.3, 7.0, 5.0 Hz, 1H), 2.12 – 1.96 (m, 1H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0, 156.6, 140.6, 133.1, 121.6, 114.2, 114.0, 55.6, 48.6, 45.6, 32.0, 23.1.

IR (Neat film, NaCl): 3360, 3077, 2962, 2927, 2060, 1693, 1512, 1504, 1455, 1394, 1315, 1299, 1246, 1182, 1170, 1124, 1111, 1090, 1034, 1005, 924, 913, 883, 825, 807, 731, 636 cm^{-1}.

HRMS (MM:ESI-APCI+): *m/z* calc'd for $C_{14}H_{17}NO_2Na$ $[M+Na]^+$: 254.1151, found 254.1155.

Optical rotation: $[a]_D^{25}$ – 0.6 ° (*c* 0.35, $CHCl_3$).

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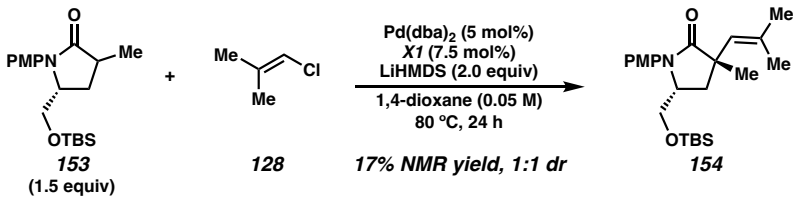
(4) In a matched/mismatched case, we observed poor efficiency of the reaction to deliver compound **154**:



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(11) Synthesis of product **152** from vinyl chloride directly would be prohibitive, as this would require a toxic gas as the electrophile and would be unlikely to exhibit asymmetric induction in a Pd-catalyzed system.

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